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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/585,429	07/07/2006	Tai-wei Ly	11582-006-999	4713

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EXAMINER	
MURRAY, JEFFREY H	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
10/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/585,429	LY ET AL.	
	Examiner	Art Unit	
	JEFFREY H. MURRAY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 12-27* is/are pending in the application.

4a) Of the above claim(s) *12,13 and 21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,14-20 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/7/2006 & 12/8/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to an election from a restriction requirement filed on July 2, 2009. There are twenty four claims pending and eighteen claims under consideration. This is the first action on the merits. Election was made **without** traverse in the reply filed on July 2, 2009. Therefore this restriction is considered proper and thus made **FINAL**.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the EPO on January 31, 2004. It is noted, however, that applicant has not filed a certified copy of the 04002144.6 application as required by 35 U.S.C. 119(b).

Specification

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Claim Objections

Claims 1-8 and 25-27 are objected to because of the following informalities: The term "imidazo[1,2-c]pyrimidinylacetic acid derivative" should be replaced by the term "compound" to avoid confusion. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 14-20 and 25-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound, composition, its tautomeric or stereoisomeric form or pharmaceutically acceptable salt thereof, does not reasonably provide enablement for any esters, hydrates or solvates within the broad Claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (United States v. Teletronics Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See Ex parte Forman 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Amount of guidance provided by Applicant.* The Applicant has demonstrated within the application how to make imidazopyrimidines. However, there is no working example of any hydrates or solvates. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However...there is no evidence that such

compounds exist...the examples of the '881 patent do not produce the postulated compounds...there is...no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that hydrates or solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that hydrates or solvates can be made, or limit the claims accordingly.

With regard to esters, applicants have demonstrated within the specification how to make esters. However, none of these esters are covered by the current set of claims. Claim 1 reads on an imidazopyrimidine with an acetic acid group in the 8-position. The only esters which applicants have demonstrated are esters of this acetic acid. These compounds would not be covered by the current set of claims as the 8-position must be an acetic acid group, no esters are permitted. In addition, esters can form at the R^1 and R^3 positions. Therefore without being specific, the examiner has no direction as to where the applicants intend this ester to form. Do they intend the ester off of the acetic acid group, which is not covered by the current set of claims? Or do they intend either the R^1 or R^3 group, both of which may form esters but no guidance has been given on how to make or use these esters? Applicants must be clear and precise. Here applicants attempt to patent "esters" with no patentable esters either described or demonstrated within the specification.

The quantity of experimentation needed to make or use the invention must be considered to determine if undue experimentation is present. With regard to quantity of experimentation needed, (note Wolff et. al., "Burger's Medicinal Chemistry and Drug Discovery," 5th Ed. Part 1, pp. 975-977 (1995) provided with this action), which

emphasizes the many experimental factors for consideration for a successful prodrug as well as the difficulty in extrapolating data from one species to another. See p.975-7. "Extensive development must be undertaken to find the correct chemical modification for a specific drug. Additionally, once a prodrug is formed, it is a new drug entity and therefore requires extensive and costly studies to determine safety and efficacy." Banker, et. al., Modern Pharmaceuticals, p.596-7. In view of all these factors undue experimentation would be required to practice the invention.

2) *Unpredictability in the art*. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish

> negative results, because these are, as opposed to positive results, never definite (and far too copious)." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

The scope of "solvate" and "hydrate" is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. Solvates cannot be predicted and there fore are not capable of being claimed if the applicant cannot properly enable a particular solvate.

> "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates. Vippagunta et. al. Advanced Drug Delivery Reviews 48 (2001) 3-26.

Many functional groups (eg. hydroxy, amino groups) present in drugs are capable at least in theory to being derivatized but determining what is a prodrug (and what is not) requires knowledge of an intended effect (i.e. modification of an undesirable property in the parent drug- poor solubility, poor bioavailability, poor shelf-life) which is never identified by the specification.

The scope of esters is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*, nor are the esters demonstrated within the specification even patentable. The choice of an ester will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which ester will be suitable for the instant invention. The

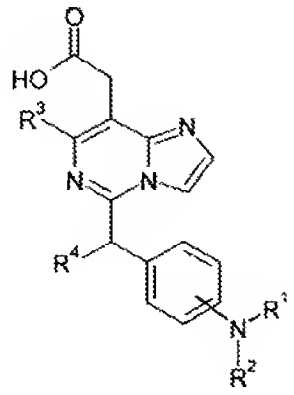
application does not provide any guidance for one skilled in the art on how the ester is converted to active compounds, by what mechanisms and at what site the ester will be activated, what *in vivo* enzymes are likely involved in cleaving the protected group, etc.

Applicants provide no reasonable assurance that any and all known esters will have the ability to regenerate in *vivo* to the instant compounds by one or more biological processes. It is not the norm that one can predict with any degree of accuracy a particular ester form of an active compound will be more soluble, more easily handled in formulations or more bioavailable without actual testing *in vivo*.

3) *Number of working examples.* The compound core depicted with specific substituents represents a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed or preventive agents. Applicant has provided no working examples of any compounds, compositions or pharmaceutically acceptable salts where the R variables were not those mentioned above in the present application.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

4) *Scope of the claims*. The scope of the claims involves all of the thousands of compounds of the following formula:



thus, the scope of claims is very broad.

5) *Nature of the invention*. The nature of this invention relates generally to a imidazopyrimidinylacetic acid derivative which is useful as an active ingredient of pharmaceutical preparations.

6) *Level of skill in the art*. The artisan using Applicants invention would be a chemist with a Ph.D. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for making these compounds or compositions or treating the diseases mentioned.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7, 8, 14-19 and 25-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as reciting an intended use. The recitation of an intended use, chemical activity, or functional description of some "additional" property for a compound (or moiety/functionality attached to a chemical core) or a composition containing same in a dependent claim, must result in a “tangible structural difference” between the product and of the independent claim and the product set forth in the dependent claim. In the absence of said structural difference between the product of the independent claim and that of the dependent claim, said dependent claim is seen to be a substantial duplicate, and said recitation is not afforded critical weight and fails to further limit the product in said dependent claim. In the instant set of claims, claim 8 fails to further limit the claims to a composition from which it depends.

Claims 7 and 14-19 recites the limitation "pharmaceutically acceptable excipients" or “excipient” in claim 6. There is insufficient antecedent basis for this limitation in the claim.

Applicants state in claim 25, “…wherein the imidazo[1,2-c]pyrimidinylacetic acid derivative is an ester of formula (I).” Neither claim 1 nor claim 25 discuss which ester is

being discussed. It is noted that both R^1 and R^3 may form an ester. Without a more definite description as to which ester is being described within the claim, examiner cannot determine the correct structure of the compound and thus claims 25-27 are indefinite. No new matter permitted. Appropriate correction required.

Double Patenting

Applicant is advised that should claim 6 be found allowable, claim 8 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

Claims 1-8, 14-20 and 25-27 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is 571-272-9023. The examiner can normally be reached on Mon.-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Mr. James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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